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Targeting Gastric Cancer Stem Cells through Developmental Pathways: Hypothesis

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A B S T R A C T

Cancer stem cells (CSCs) have been defined as a unique subpopulation in tumors, endowed with the capacity to initiate tumor progression, and maintain self-renewal as well as metastatic potential. Recently, more evidences strongly indicate the existence of CSCs in solid tumors of wide variety of organs such as breast, brain and stomach. Recent studies suggest that a special subpopulation of gastric cancer cells with specific marker namely CD44, shows spheroid colony formation in serum free media in vitro, as well as tumorigenic capacity in immunodeficient animal model in vivo. In addition, current evidences indicate that one of the major reasons for failure of chemotherapy and radiotherapy is the existence of CSCs with resistant mechanisms against current therapeutic strategies. Growing evidence recommended that pathways which are responsible for regulation of normal stem cell self-renewal and differentiation may also represent regulatory roles in maintenance of cancer cells and CSCs. Two major therapeutic approaches for elimination of CSCs are differentiation therapy and inhibition of important pathways involved in maintenance of CSCs such as notch signaling.It is hypothesized that with inhibition of notch signaling by means of DAPT(gamma-secretase-inhibitor), silencing Ral pathway as well as inducing differentiation by means of all-trance retinoic acid (ATRA) in $CD44^{+}$ gastric cancer stem cells, we can target this small population and eventually eliminate them by sensitizing these cells to chemotherapy and radiotherapy as well as induction of apoptosis in them.

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Introduction

Cancer is a kind of genetic disease that causes some pivotal changes in three kinds of genes, which are responsible for tumor development including oncogenes, tumor suppressor genes and stability genes. These alterations in genes are what make a normal cell to disregard growth controlling signals and constitute a tumor that finally leads to the destruction of organisms [1, 2]. Since carcinogenesis is a multi-step process, cancer can develop in a series of steps through accumulation of molecular changes. Progression of pre-invasive disease to invasive disease depends on the amount of such changes. Currently, most research on human malignancies is focused on the molecular and cellular analysis of the tumor mass [3].

Recently, evidences suggest that only small subpopulation of cancer cells within some tumors are long-lived with specific ability to sustained self-renewal and tumor formation in vivo. For the first time, cells with these criteria were reported in acute myeloid leukemia, but similar populations were soon identified within various solid tumors such as breast, brain and lung cancers [4]. In other words solid tumors, similar to aberrantly developed organs and tissues, are complex collections of heterogeneous cells consisting neoplastic cells, vasculature cells, inflammatory cells, fibroblasts and stromal elements. This small population which due to its stem cell-like characteristics, is defined as cancer stem cell (CSCs) also known as cancer initiating cells (CICs) and tumor stem cells (TSCs) [5]. The concept of cancer stem cell emerged about 150 years ago, but the first proof of CSC existence dates back to 1994, when John Dick and his colleagues were able to successfully identify and purify human acute myeloid leukemia initiating cells with distinct stem properties. Indeed, this concept arose from significant resemblances between the self-renewal mechanism of normal organs and continuous proliferation in cancer [3].

Today CSCs hypothesis suggests that these cells are small subset of cancer cells that have the ability of unlimited growth, self-renewal as well as differentiation into more differentiated cancer cell types. Unlike other differentiated or differentiating cancer cells which form the bulk of the tumor and cannot generate new cells, CSCs with self-renewal and unlimited growth properties can form new tumor in immune deficient animal models. In addition, it was demonstrated that these cells are able to regenerate and repopulate the tumor even after the mass removing of malignant tissue by chemotherapy or radiotherapy [6].

With many advances in stem cell biology and rapid development of technologies for isolation and characterization of CSCs as well as the understanding of signaling pathways involved in their self-renewal and differentiation, we can observe considerable impact on our current perception of cancer diagnosis, management and treatment options.

Cancer Stem Cell: definition and characterization

All tissues in our body originate from organ-specific stem cells that possess the self-renewal capacity as well as differentiation into all lineages of the tissue they reside in. Stem cells are unique population with three specific properties including a) self-renewal, b) capacity to develop into multiple lineage, and c) potential to extensive proliferation. Nevertheless, the self-renewal is more notable; because aberrant increasing of this property is highly relevant to oncogenesis and malignancy [7]. As we know tumors are heterogeneous regarding their cell phenotype and proliferation potential. Indeed, CSCs are a small population (<1%) of the overall cancer cells in tumor mass that have the capacity to proliferate extensively and form new tumors [1]. Given these features, these cells are the main reason for tumor relapse, therapeutic failure, drug resistance and metastasis. CSCs may undergo symmetrical or asymmetrical cell divisions. Symmetric division leads to the production of two identical daughter CSCs, whereas in asymmetric division each CSC divides into one daughter CSC and one differentiated cell. These kinds of cell divisions can result in increasing the number of CSCs followed by the tumor growing and tumor expansion [8]. Recent evidence suggests that CSCs

may arise by multiple mutations from normal stem cells, progenitor cell (also known as transit-amplifying cells) or more differentiated cells. These mutations of genes occur as a result of their gene instability or oncogenes-induced plasticity. Moreover, accumulation of mutations which followed by genetic or epigenetic instability cells enable them to acquire the ability of self-renewal and tumorigenicity [9]. In other words, the origin of CSCs is still an area of ongoing research. There are different theories about the origin of CSCs, which have pros and cons. One of these theories claims that CSCs generation is a consequence of mutation occurrence in developing stem or progenitor cells. According this theory, each mutation in developing stem population is expanded by daughter stem cells. These descendant stem cells with specific mutation are then much closer to make a tumor. Based on another theory, mutation occurrence in adult stem cells, especially in tissues with high rate of cell turnover (such as skin and gut) is an initiating step in tumor formation. Frequent cell divisions of these stem cells in conjunction with extremely long lifespan, create the ideal set of circumstances for accumulation of mutation, and aggregation of these mutations is the primary factor to initiate cancer. A third possibility claims that mutated cells have potential to de –differentiate and acquire stem cell like characteristics. This theory suggests that any cell might become a cancer stem cell [10].

Another property of CSCs is their invasiveness. Epithelial-mesancheymal transition (EMT) is one the mechanisms that can generate CSCs with invasive and metastatic phenotype. In this multi-step mechanism epithelial cells were transformed into fibroblast-like and motile cells. Eventually, by this feature, cancer cells acquire the capacity to invade, migrate and disseminate [11].

Cancer Stem Cell: Isolation

The isolation and identification of small population of CSCs from mass tumor tissue or cell line is an important issue in this field. The most widely utilized method for identifying CSCs is based on specific cell surface marker such as CD133, CD44, and CD24.However, it should be noted that the expression of surface markers in CSCs and normal stem cells depends on the type of tissue. For instance Al-Hajj et al study was demonstrated that $CD44^+$, $CD24^-$ phenotype cells in human breast cancer were tumorigenic whereas Li and his colleagues indicated that $CD44^+$, $CD24^+$, ESA^+ phenotype cells in pancreatic cancer can form a new tumor [2]. Moreover, according to Yan et al, cells with $CD45^-$, $CD90^+$, and $CD44^+$ phenotypes in liver cancer are tumorigenic [6]. Additionally, these surface markers that are used for isolation and purification of CSCs may express in both CSCs and some normal stem cells even in normal tissues [5, 12].

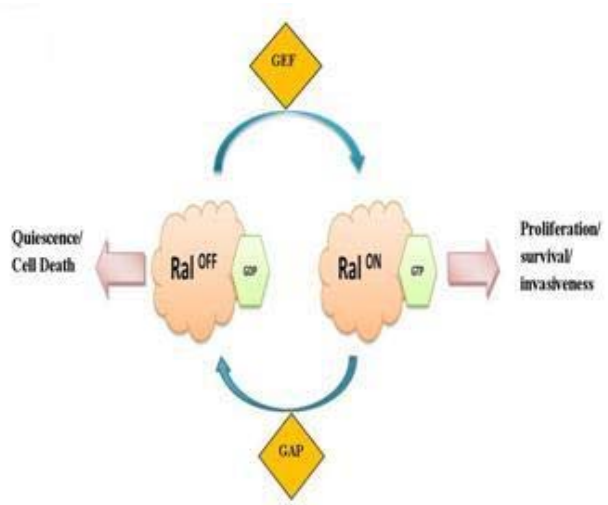
Cancer Stem Cell Therapy

Chemotherapy and radiotherapy are two traditional and common therapies to hit cancer cells. However, drug resistance and systemic or local toxicity are considered as two main drawbacks of these methods to achieve their missions. It seems these methods can shrink primary and metastasis tumors but such effects are usually transient. So both serious side effects and tumor relapse are inevitable reasons for failure of traditional therapies.

Emerging evidences revealed that one potential reason for failure is the existence of CSCs in tumor mass. These therapeutic methods are unable to kill CSCs. In other words, it suggests that CSCs with some mechanisms such as relative dormancy/slow cell cycle kinetics, high capacity for DNA repair, high expression of multiple drug resistance membrane transporters(e.g., ABC transporters), high expression of anti- apoptotic proteins and the microenvironment conditions (hypoxia ,acidosis),can with stand traditional therapies. Therefore, it is important to use the combination of traditional chemotherapy and radiotherapy with new strategies targeting CSCs in order to provide a high-efficient and low toxic treatment and prevent tumor recurrence [13]. Understanding the cellular signaling which controls stem cell proliferation and differentiation could lead to the development of new anticancer strategies. These new therapeutic strategies should be properly designed to target CSCs by inducing the differentiation and eliminating the maintenance of the stem cell potency. In addition,

targeting some signaling pathways which involved in maintenance of stem cell property might be useful to transform malignancies into benign tumors. Thus, differentiation therapy and targeting the molecular signaling pathways might be two novel strategies targeting CSCs population and eliminating them. Differentiation therapy in oncology is broadly used for targeting CSCs [1, 2, 14]. Since CSCs population is undifferentiated in comparison with cancer cells, this kind of therapy can force CSCs to differentiate and lose their self-renewal property. The most thoroughly examined agents in clinical practice are retinoic acid (RA, vitamin A), and its analogous (Retinoid). These agents can regulate differentiation and proliferation of epithelial cells and they can subvert the malignant progression process through transducing of signal modulation mediated by retinoic acid receptors (RAR) and retinoic X receptors (RXR). Campos *et al* demonstrated an anti-tumor effect of all-trans retinoic acid (ATRA) on stem-like glioma cells (SLGC) *in vivo* and *in vitro* and efficacy of this agent on differentiation of these cells [15]. In another study Ginestier et al revealed that ATRA treatment has induced the differentiation of breast CSCs resulted in a significant reduction of breast CSCs population. Moreover, acute promyelocytic leukemia has become a curable disease through using the combination of chemotherapy and ATRA-based induction therapy. Retinoid could also be used for chemoprevention. It can induce differentiation in precancerous cells and is used as a chemo-preventive agent for head and neck and lung cancers. Given these result, it seems that retinoic acid might be a therapeutic strategy for targeting CSC population [16, 17].

Another considerable strategy is targeting CSCs through pathways that control self-renewal and cell fate decision of undifferentiated pluripotent cells. As evidences have revealed, any deregulation or aberrant activation of these key pathways may result in the formation of CSCs which induce tumorgenesis [18]. One of the important pathways is Notch. Notch signaling pathway has significant role in cell-cell communication and cell fate decision during embryonic development and adult life. Moreover, this pathway is involved in stem cell proliferation, differentiation and apoptosis, however, its role in tumorgenesis is context-dependent and can be either oncogenic or oncosuppressor [19].Notch proteins may have oncogenic activities in most human cancers including cervical, lung, colon, head and neck, prostate, gastric, pancreatic cancer, also they may act as tumor suppressive in skin, hepatocellular carcinoma and SCLC. Notch proteins are single-pass trans-membrane receptors. This pathway is activated through ligand receptor interaction of four receptors Notch 1-Notch 4 and five ligands, Delta1, 3, 4 and jagged 1, 2. Upon ligand binding, Notch is cleaved by gamma-secretase complex to release its intracellular domain (NICD) from the cell membrane. NICD translocates into the nucleus to act as a transcription factor resulting in the expression of multiple target genes. Blocking the proteolytic process is one of the most efficient and practical methods to inhibit Notch signaling pathway. DAPT (N-[N-(3, 5 difluorophenyl -L-alanyl)] - Phenylglycine t-butyl ester) is a type of γ-secretaseinhibitor (GSI) that can efficiently block cleavage activity of γ-secretase. Fan and his colleagues indicated that using the gamma-secretase inhibitors (GSIs) to block Notch pathway in glioblastoma and $CD133^{+}$ cells in medulloblastoma lead to reduced neuro sphere growth and clonogenicity in vitro[19, 20]. Ral signaling pathway is recognized as one of the most important pro-oncogenic signaling cascades in human malignancies [21]. Ras-like (Ral) guanyl nucleotide –binding proteins, RalA and RalB are members of Ras family G-proteins. They cycle between inactive GDP-bound and active GTP-bound conformation [22]. Two classes of regulatory proteins GEFs and GAPs help to turn Ral on and off , respectively and are critical for appropriately balancing normal Ral activity[21]. Ral a multifunctional protein, exerts fundamental roles in cell biology including, intracellular membrane trafficking, transcription cell migration, apoptosis, cell proliferation and oncogenesis [23].



Schema 1. Targeting Gastric Cancer Stem Cells through Developmental Pathways: Hypothesis

Hypothesis

Gastric cancer is one of the most common and lethal malignancies with high mortality rate in the world. [24]. The cancer stem cell hypothesis is a promising new paradigm that could remarkably impact on diagnosis and management of malignancies. Routine cancer treatment such as surgery, chemotherapy, radiotherapy have focused on killing Proliferous and differentiated cells, while, due to the survival of CSCs ,these strategies are not successful. CSCs population is identified and purified by specific cell surface markers. Among different markers, CD44 is widely used for isolation of CSCs from solid tumors [3].CD44 is a trans-membrane glycoprotein, which plays important roles in malignant behavior of several human cancers and it was reported as a cell surface marker to identify gastric cancer stem cells in gastric cancer cell lines [12, 24, 25].

Recent observations have demonstrated the considerable role of Ral protein in development and progression of malignancies. Over activation of this pathway has proven in breast, bladder and colorectal cancers, as well as nerve sheath tumors [26, 27]. Farassati *et al* have demonstrated that inhibition of Ral A by gene specific silencing resulting in reduction of cell proliferation, invasiveness and *in vivo* tumorgenesis as well as inducing apoptosis/necrosis in non-small cell lung cancer (NSCLC).Furthermore, Overactivation of RalA in $CD44^+$ lung CSCs introduce this pathway to be involved in the biology of CSCs [28]. Given these consequences, Ral A may not only be of receiving attention a valid direct therapeutic target , but may also be accounted for developing strategies to enhance chemo-responsiveness of cancer cells[21]. On the basis of these results, it is hypothesized; gene specific silencing of Ral A in $CD44^+$ gastric CSCs may lead inducing apoptosis as well as decreasing proliferation in these cells. Moreover, if over activation of Ral A is an important factor in the viability and chemo-resistance of $CD44^+$ gastric CSCs, its silencing should be adversely affect the viability and chemo-responsiveness of these cells.

Emerging evidences suggest that Notch signaling is involved in controlling the progression of gastric cancer .The expression of Notch-1 was found to be closely associated with tumor size, differentiation grade, depth of invasion in gastric cancer[29,30]. Given these results, it seems that deregulation or improper activation of Notch signaling is a key feature of many human cancers such as gastric cancer [30]. Previously the role of Notch signaling in maintenance of CSCs has been shown in glioma [31]. As a result, we would declare that inactivation of Notch pathway by novel approaches may have significant impact on cancer therapy. Notch signaling activated through the activity of γ-secretase which became one of the most promising targets in inactivation of Notch pathway. γ- secretase is a critical component of Notch signaling pathway at cell membrane [32]. DAPT (N-[N-(3, 5 difluorophenyl -L-alanyl)] - Phenylglycine t-butyl ester) is a type of γ-secretase inhibitor (GSI) that can efficiently block cleavage activity of γ-secretase which is responsible for releasing Notch intracellular domain (NICD). Treatment with DAPT resulted in suppressing medulloblastoma cell growth, G0-G1 cell cycle arrest and apoptosis in T-ALL (T-cell acute lymphoblastic leukemia) animal models [33]. Also the combined exposure to irradiation and DAPT led to decrease in the self-renewal ability (neurosphere formation) and reducing $CD133^+$glioblastoma cells significantly [32, 34, 35]. Taking these results together, it is hypothesized

that inhibition of Notch signaling by DAPT in $CD44^+$ gastric CSCs may have significant contribution in reduction of tumorigenicity and self-renewal ability of these cells. Previously stated that, differentiation therapy is one of the therapeutic strategies to eliminate CSCs. All-trans retinoic acid (ATRA), a derivative of retinoic acid [15], currently is being utilized in various kinds of hematological malignanciesas potential chemo-preventive and chemotherapeutic agent due to its anti-proliferative, anti-oxidant, pro-apoptotic and differentiation effects [16,17]. Observations indicated that ATRA is able to induce differentiation in $CD133^+$glioma CSCs. According to these results, it can be concluded that ATRA may have therapeutic potency through differentiation of CSCs and rendering them sensitive to targeted therapy. Given these results, it is hypothesized that ATRA may have potency to induce differentiation in $CD44^+$ gastric CSCs. By this way; overall population of CSCs may be sensitized to chemotherapeutic agents. In addition high doses of ATRA may lead to induction apoptosis in $CD44^+$ cells. Briefly, it seems that concomitant use of Notch inhibitor DAPT and ATRA may lead to overcome the self-renewal ability, induce apoptosis, reduce $CD44^+$ CSCs cell growth and sensitize them in order to have better response against traditional therapeutic methods (see scheme).

Conflict of Interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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